Potential new therapy could reduce dangerous post-heart-attack inflammation

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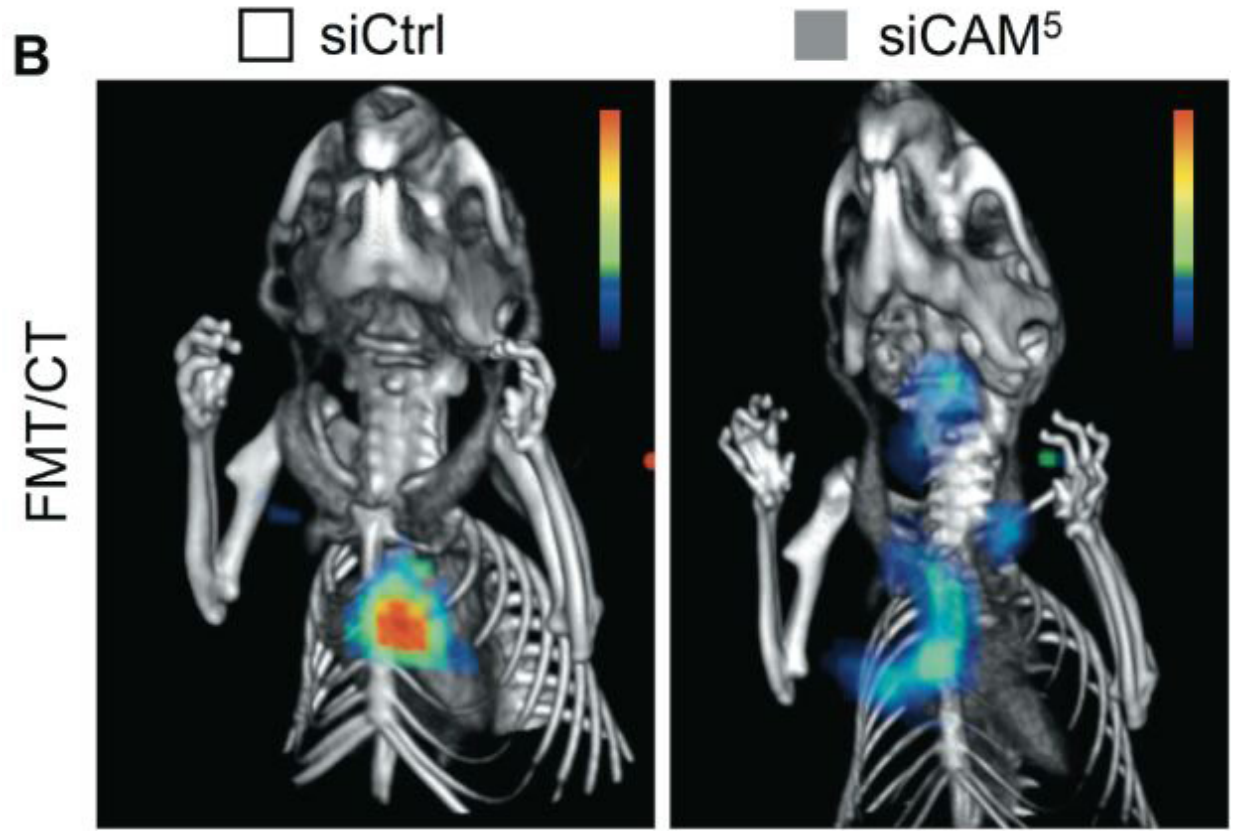

Aortic root protease activity significantly decreased in mice treated with siCAM5 , as shown by fluorescence molecular tomography (FMT)/computed tomography (CT). Credit: H. Sager et al., Science Translational Medicine (2016)

A new study led by investigators at Massachusetts General Hospital

(MGH) has identified a mechanism behind the surge in cardiovascular inflammation that takes place after a heart attack. Working with collaborators from the Massachusetts Institute of Technology (MIT), the team also developed a potential strategy for suppressing inflammation within atherosclerotic plaques, the first approach that targets the immune system's contribution to cardiovascular disease. Their work in animal models of heart disease is described in a *Science Translational Medicine* paper.

"We found that activation of sympathetic nerve fibers within the arterial lining, which takes place in response to a heart attack, leads to increased expression of adhesion molecules on the endothelial cells lining atherosclerotic plaques. Those molecules both attract inflammatory white blood cells and cause those cells to stick to the plaques, increasing the risk for another heart attack," says Matthias Nahrendorf, MD, PhD, of the MGH Center for Systems Biology, co-senior author of the report. "We also found that we can shut off the expression of those adhesion molecules by means of nanoparticle-delivered RNA interference."

A 2012 *Nature* study led by Nahrendorf was the first to show that an experimentally induced heart attack led both to the increased generation of monocytes and other inflammatory cells and to the accumulation of those cells in existing atherosclerotic plaques. These immune cells attach themselves to and penetrate within endothelial cells by means of adhesion molecules on the surface of endothelial cells. In the current study, a series of experiments with a mouse model of atherosclerosis revealed that activity of sympathetic nerve fibers within the animals' aortas was responsible for the increased expression of several adhesion molecules after a heart attack.

The investigators then tested whether small interfering RNA (siRNA), which precisely targets the production of specific proteins, could be used to reduce the expression of adhesion molecules on endothelial cells. This

was accomplished by means of nanoparticles targeting all five adhesion molecules known to be expressed at sites of arterial inflammation. A 2011 study by Nahrendorf and several members of the current research team - including co-senior author Daniel Anderson, PhD, of MIT - had utilized siRNA nanoparticles to target a single inflammatory receptor protein.

Targeting all five adhesion molecules not only reduced the recruitment of inflammatory immune cells to aortal plaques in the animals, it also lowered the expression of inflammatory proteins called cytokines and enzymes that contribute to the rupture of arterial plaque that triggers a heart attack. Applying the treatment before an induced heart attack reduced subsequent inflammatory changes, while treatment after a heart attack cut the recruitment of inflammatory cells in half and improved the recovery of heart function. A nanoparticle targeting a single adhesion molecule was significantly less effective.

"No current cardiovascular therapy targets the recruitment of immune cells to plaques, although that is the primary contributor to future ischemic events - those caused by a cutoff of blood supply," says Nahrendorf, who is an associate professor of Radiology at Harvard Medical School. "Once this approach is translated, we hope it may help to 'cool down' inflammation in patients with ischemic organ injury, protecting cardiac patients from a second heart attack and helping the heart to recover. We now need to test this approach in larger animals and confirm its safety before it can be tested in human patients."

More information: "RNAi targeting multiple cell adhesion molecules reduces immune cell recruitment and vascular inflammation after myocardial infarction," DOI: 10.1126/scitranslmed.aaf3634

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